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EXAMINER	
BAUSCH, SARAE L	

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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/073,464	TIEDJE ET AL.	
	Examiner	Art Unit	
	Sarae Bausch	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-6, 8-14 are pending in the instant application. Claim 7 and 15-21 have been canceled. This action is written in response to applicant's correspondence submitted 03/28/2007. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented, as necessitated by amendment, or are reiterated from the previous office action. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is Final.**

Withdrawn Rejection

2. The rejections of claims 3 and 11, under 35 U.S.C. 112, second paragraph, made in section 4 of the previous office action mailed 11/30/2006, is withdrawn in view of the amendment to the claims.

Maintained Rejections

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1-6 and 8-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Hogan et al. (US Patent 6821770 filing date 03/03/1999). This rejection was previously presented in section 6 of the office action mailed 11/30/2006 and is reiterated below.

With regard to claim 1, 5 and 9, Hogan et al. teach a method identifying bacteria by hybridizing a released polynucleotides from a biological sample to a probe matrix. Hogan et al. teach the released polynucleotides are amplified prior to hybridization (see column 6, lines 44-60). Hogan et al. teach the probe matrix includes probes arrayed on a testing device where each locus specifically hybridizes nucleic acid from one or a plurality of microorganisms species (see column 11, lines 1-13). Hogan et al. teach a preferred collection of species probes would be E. coli, Staphylocoous aureus, Candida albican, Pseuomonas aeruginosa, and Streptococcus pneumoniae (reference DNA from four strains of reference bacteria) (see column 30, lines 14-20). Hogan et al. teach labeling of probes and polynucleotides with fluorescent labels that produce light at different wavelengths (see column 36, lines 40-45). Hogan et al. teach a plurality of nucleic acid probes are physically combined at a single locus in a testing device (see column 29, lines 24-32) and teach identification of bacteria is determined by hybridization of the sample to the testing format, which includes a DNA chip (claim 5) (see column 36, lines 1-10). Hogan et al. teach calculating the hybridization signal to determine the identity of the bacteria (see column 37, lines 5-25).

With regard to claim 2-3 and 10-11, Hogan et al. teach rapid clinical diagnosis of microbial infection including infections of the oral cavity, blood, urinary tract which include samples obtained from subjects (see column 13, lines 38-50).

With regard to claim 4 and 12, Hogan et al. teach identification of one or more microbes in environmental samples (see column 13, lines 58-62).

With regard to claim 6 and 14, Hogan et al. teach an algorithm that correlates the profile of the hybridization data with identities of organisms and performs a quantitative analysis to provide a basis for determining whether a numerical result from a hybridization procedure is positive or negative (see column 38, lines 8-28) and teaches normalization of the hybridization data (see column 44, lines 20-24) (calculating a statistical analysis).

With regard to claim 13, Hogan et al. teach producing hybridization profiles of the probe matrix hybridization (hybridization profile of test and reference bacteria) (see column 37, lines 5-24).

Response to Arguments

5. The response traverses the rejection on pages 6-7 of the response mailed 03/28/2007. The response asserts on page 6 that the examiner has pointed to several citations within Hogan in an attempt to find all the Applicants claimed elements and asserts that the examiner is clearly using hindsight by picking and choosing within Hogan et al. The response further asserts that the examiner has focused on what rather than how and that the claims are method claims not product claims. This response has been thoroughly reviewed but not found persuasive. The entire disclosure of Hogan et al. anticipates the claimed invention. Several citations throughout Hogan et al. were relied upon to address the specific limitations of the claims and to help direct

applicant to the specific teachings of Hogan that anticipated the claimed invention. The specific cited references within the rejection are not a "pick and choosing" as referred to by applicant as the citation references are merely cited as an aid for applicant. Furthermore, applicant cited, on page 6 of the response, in re Fritch to support the assertion of hindsight reasoning in, however in re Fritch addresses rejections made under 103 and the use of hindsight reasoning to pick and chose among disclosures in the prior art (more than one disclosure), which is not applicable in the instant case as the claims are rejected under 102(e) as being anticipated by one disclosure, in its entirety. Additionally, it is noted that the rejection of record focused on how rather than what, see rejection above. For example the rejection recites Hogan et al teach calculating a ratio of the hybridization signal to determine the identify of the bacteria, which is not focused on what rather than how.

In response to applicant's argument that the present invention is designed to avoid cross hybridization assays and that Hogan presents a very complicated method involving simultaneous assessment of multiple cross hybridizations which fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., avoiding cross hybridization) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The response asserts that Hogan requires an integrated systematic method that requires at least seven pair wise comparisons to even attempt a species identification and does not guarantee success. The response asserts that Hogan teaches that a species identification will not necessarily happen. These assertions have been thoroughly reviewed but not found persuasive.

The claims are not limited to a specific number of comparisons to attempt a species identification. The claimed method is a method for identifying bacteria "comprising" which allows for additional method steps, including additional hybridization and comparison steps. Additionally, Hogan et al. does teach that species identification does occur (see column 37, lines 5-25).). The indication of positive or negative results hone Hogan's results of hybridization into the species specific detection. The patent is not directed to results that work versus fail as appears to be suggested by the response. The negative results of Hogan provide clear guidance to the artisan the results of the assay.

The response asserts that Hogan collects a series of yes/no data that is compared to a pre-constructed database and Hogan et al. teach a method wherein data collection is limited to the collection of binary information and merely compares linear patters produced by each address level and does not calculate any signal ratios. This response has been thoroughly reviewed but not found persuasive. The claims are not limited to the amount of bacteria present, the claims merely require identification of a bacteria, in which case a yes/no response would anticipate the claimed invention. Furthermore, Hogan et al. does teach calculating the ratio of the hybridization signal, which includes fluorescence signals, see column 38, lines 7-17. Hogan teaches "the processor may perform a quantitative analysis to provide a basis for determining whether a numerical result from a hybridization procedure is positive or negative. For example, a positive result would be indicated when the hybridization value is greater than a lower threshold value, and is at least several fold greater than the negative control hybridization value." As clearly evidenced by the comparison to a control and then to a threshold, Hogan teaches calculating a ratio to determine the species of the test bacteria. The response suggests that

Hogan merely compares linear patterns produced by each address. This assertion is not supported by the passage provided above. Thus, Hogan teaches a process that performs a quantitative analysis to provide a basis for determining a numerical result from a hybridization procedure is positive or negative and teaches that a positive result would be indicated when the hybridization value (reference/control signal) is greater than a lower threshold value (reference signal). Hogan et al. teach calculating a numerical result, i.e. calculating a ratio, and determining if that ratio is positive or negative.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

6. Claims 1-6 and 8-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Gingeras et al. (US Patent 6228575 filed 02/07/1997). This rejection was previously presented in section 7 of the office action mailed 11/30/2006 and is reiterated below.

With regard to claim 1 and 9, Gingeras et al. teach a method of oligonucleotide array for speculating and phenotyping organism by providing an array of known locations on a substrate comprising a plurality probes to reference DNA sequences hybridizing target nucleic acid sequence to array and based on hybridization pattern identifying the genotype of the first organisms(see column 3, lines 1-13 and column 4, lines 7-13). Gingeras et al. teach amplification of nucleic acid sample prior to hybridization (See column 8, lines 34-37) (providing amplified genomic sequences). Gingeras et al. teach hybridized nucleic acid are detected by detecting one or more labels attached to the sample nucleic acids and include fluorescein labels (see column 8, lines 46-57) (labeled DNA with a fluorescent dye). Gingeras et

al. teach the screening method allows one to build up a data base of hybridization patterns corresponding to different species. Gingeras et al. teach identifying mycobacterium species by measuring fingerprint data (hybridization pattern on array) (see column 30, lines 65-67) by a collection of samples and based on these measurements a systematic way to predict species of each member of the collect by comparing the signal produced by the target at each hybridization site compared to the signal produced by Mt rpoB (see column 31, lines 1-5). Specifically, Gingeras et al. teach hybridization analysis of 7 mycobacteria species (reference samples) and teach that a reference sequence can be sequence of nucleotides, DNA (see column 12, lines 51-53 and column 34, lines 45-51). Gingeras et al. teach fluorescently labeled amplicons from mycobacteria species hybridized to a DNA chip and comparing the hybridization pattern to amplicons hybridized to the DNA chip from M. tuberculosis (test bacteria) (see column 35, lines 15-25 and table 4). Gingeras et al. teach analyzing the fingerprint pattern of each species followed by classification analysis (calculating the hybridized DNA fluorescent dye signal and reference DNA fluorescence to determine identity) (See column 36, lines 35-51).

With regard to claim 2-3 and 10-11, Gingeras et al. teach assaying biological samples, which refers to a sample obtained from an organism or clinical sample from a patient (See column 8, lines 22-34).

With regard to claim 4 and 12, Gingeras et al. teach assaying biological samples obtained from an organism (environmental sample) (see column 8, lines 22-25).

With regard to claim 6, 13, and 14, Gingeras et al. teach hybridization patterns (producing hybridization profiles) correlated to species determination using mathematical pattern

recognition algorithms (calculating by statistical analysis) (see column 30, lines 5-67 and column 31, lines 1-67).

Response to Arguments

7. The response traverses the rejection on pages 8-9 of the response mailed 03/28/2007. The response asserts that a hindsight arugment has been provided. It is noted that this rejection is under 102 which is not subject to hindsight.

The response asserts that Gingeras et al. describes a repetitive hybridization technique that is dependent upon polymorphisms within a particular sequence. The response asserts that Gingeras specifically points out that a single hybridization step will be insufficient to differentiate between a target and reference sequence. The response asserts that Gingeras does not teach a simple and direct competitive inhibition assay between a labeled reference probe and a labeled reference target. This response has been thoroughly reviewed but not found persuasive. The response asserts that Gingeras et al. describes a repetitive hybridization technique that is dependent upon polymorphisms within a particular sequence. The response asserts that Gingeras specifically points out that a single hybridization step will be insufficient to differentiate between a target and reference sequence. The response asserts that Gingerase does not teach a simple and direct competitive inhibition assay between a labeled reference probe and a labeled reference target. This response has been thoroughly reviewed but not found persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., single hybridization step and a simple and direct competitive inhibition assay between a labeled reference probe and labeled reference target) are not recited in the rejected claim(s). Although

the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims are drawn to a method of identifying a bacteria comprising hybridization said target DNA and said reference DNA on said plurality of arrayed elements, however the claims are not limited to a single hybridization step as the claims are drawn to a method "comprising" which allows for additional process steps. Additionally the claims are not limited to a simple, direct and single step competitive hybridization assay.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-5, 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuiper et al. (Current Opinion in Biotechnology, 1999, 10:511-516) and Greisen et al. (J.Clin. Microbial. 1994, vol. 32, pp 335-351). It is noted that this rejection was previously presented in section 6 of the previous office action mailed 07/01/2005 and has been maintained for reasons of record in the previous office action and is reiterated below.

Kuiper et al. teaches producing a specific DNA array for the rapid identification of

pathogens and spoilage bacteria (instant claim 3-4, 11-12) (see page 512, 2nd column, 2nd paragraph). Kuiper et al. teaches producing microarrays by spotting amplicon of each ORF annotated in the genome sequence of interest on a defined support material, preferably glass-slides. Kuiper et al. teaches fluorescently labeled cDNA is used for hybridization to the DNA arrays and signal detection by confocal laser scanning (instant claim 7 and 11) (see page 512, 2nd column, 1st paragraph). Kuiper further exemplifies that different cDNA strains can be differentially labeled and used in one combined sample for hybridization providing the possibility of multiplexing and allowing for several different cDNA samples (see page 512, 2nd column, 1st paragraph). Kuiper et al. does not teach the use of at least four strains of reference bacterial species.

Greisen et al. teaches a method of detecting DNA for the identification of over 60 different strains representing 18 different bacterial species found as pathogens (instant claim 3 and 11) or presumptive contaminants in human CSF (see page 336, 1st column, 1st paragraph). Greisen et al. exemplifies amplifying DNA, followed by gel electrophoresis of amplified products, and blotting the gel onto a Pall Biodyne membrane and fixing the DNA to the membrane by a UV crosslinker (amplified genomic DNA arrayed on a solid support, microchip) (instant claim 5) (see page 336, 1st column, last paragraph cont'd to 2nd column). Greisen et al. teach probes of target DNA and reference DNA labeled with ^{32}P (see probe hybridization, page 338 and table 3) and hybridization of target DNA probes and reference DNA probes hybridized to DNA blots in 5xSSPE. Greisen et al. teach up to 12 meningitis and contaminant probes (reference and test DNA) tested against seven major bacterial species causing meningitis and identification of bacteria in CSF based on the hybridization pattern of each probe (instant claim 8

and 13) (see page 346, 2nd column, last two paragraph and table 4). Greisen et al. teaches that the use of the panel of probes would enable a single CSF sample to obtain multiple probe hybridization results and form a more rapid and sensitive means of detecting bacteria in clinical samples (see page 350, 1st column, last paragraph). Greisen et al. does not teach co-hybridizing target and reference DNA in a single step or the use of fluorescence detection for hybridization.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have improved the method of identification of pathogens using fluorescently labeled cDNA probes as taught by Kuiper et al. to include the testing of at least seven bacterial species causing meningitis by using up to 12 meningitis and contaminant probes as taught by Greisen et al. The ordinary artisan would have been motivated to use multiple probes, comprising up to 12 meningitis and contaminant probes as taught by Gresien et al. in the DNA microarray method taught by Kuiper et al. because Kuiper et al. suggests using different cDNA strains differentially labeled to be used in one combined sample for hybridization. Furthermore, the ordinary artisan would have had a reasonable expectation of success that using up to 12 different probes to test against seven major bacterial species that cause meningitis could be used in the method of Kuiper et al. because Kuiper et al. suggests using different cDNA strains in one sample for multiplexing and allowing for analysis of several different cDNA samples at one time.

Furthermore, it would have been prima facie obvious to improve the method of detection of bacteria in a sample using southern blot hybridization as taught by Greisen et al. to include co hybridization of probes in one combined sample and fluorescence detection hybridization as taught by Kuiper et al. The ordinary artisan would have been motivated to improve the method

of the southern blot hybridization method as taught by Greisen et al. to include a more rapid, automated method of multiplexing for the identification of pathogens in bacteria as taught by Kuiper et al. because Kuiper et al. suggests using different multiple labeled probes for combining several different cDNA sample for the possibility of multiplexing. Furthermore, the ordinary artisan would be motivated to use fluorescent-labeled probes to eliminate the use of radioactivity, as fluorescence in non-radioactive. The ordinary artisan would have had a reasonable expectation of success that the use of fluorescent-labeled probes to detect pathogens could be used in the method of Greisen et al. because Kuiper et al. teach the use of fluorescent-labeled probes hybridizing to a sample for the detection of pathogens. The ordinary artisan would have had a reasonable expectation of success that the use of co hybridizing probes in a single step could be used in the method of Greisen et al. because Greisen et al. teaches the use of panel of probes that would enable the use of a single CSF sample to obtain multiple probe hybridization results and form a more rapid and sensitive means of detecting bacteria in clinical samples.

Response to Arguments

10. The response filed 03/28/2007, pages 10-12 traverses this rejection. Attorneys arguments have been fully considered but are not persuasive for the reasons that follow.

The response assert that there is no motivation to combine the art. This response has been thoroughly reviewed but not found persuasive. The response does not state why there is no motivation to combine the art, however one of ordinary skill in the art would have been motivated to combine the references because both references have the same end result of identification of bacterial species. Furthermore, Kuiper exemplifies that different cDNA strains can be differentially labeled and used in one combined sample for hybridization providing the

possibility of multiplexing and allowing for several different cDNA samples (see page 512, 2nd column, 1st paragraph). Furthermore, Kuipers, in its entirety, teaches DNA microarray analysis of wild type and mutant strain cDNAs by differentially labeling and combining the sample for hybridization and multiplexing (see column 2, 1st paragraph, page 512) and further teaches that specific DNA microarrays can be developed for rapid identification of pathogens and spoilage bacteria. In the instant case, Kuipers et al. teach that fluorescently labeled DNA from two different samples is successful for analysis of DNA hybridization and distinguishing (identifying) mutant and wild type strains and Kuipers et al. further teaches that DNA microarray analysis can be developed for rapid identification of pathogens. Therefore Kuipers and Greissen teach that identification of bacteria by detection of hybridization of multiple references species can be identification by DNA microarray analysis of fluorescently labeled probes and give direction as to which choice will be successful.

The response asserts that the Examiner is reminded that "identification" can occur at many levels and asserts that Kuiper does not specify what kind of identification is contemplated or what might be involved to differentiate the various levels of identification and therefore does not teach identifying a bacterial species. This response has been thoroughly reviewed but not found persuasive. The claims do not require different levels of "identification", the claims merely require identifying a bacteria which is taught in Kuipers et al. and Griesen et al.

The response asserts Griesen et al. does not provide any detailed description for a method to identify a bacterial species using microarray technologies. The response states that Griessen does not teach the conditions necessary to achieve an effective high throughput array assay. This response has been thoroughly reviewed but not found persuasive. It is noted that Griessen et al.

is not being relied upon to teach identifying a bacterial species using microarray technologies, Kuipers and Griesen are cited as teaching the claimed invention. Furthermore, it is noted that the claimed invention is not drawn to a method of achieving an effective high throughput array assay, the claimed merely require identification of a bacteria using a hybridization assay and a microarray and not a method of a high throughput array assay.

The response asserts that even if the Examiner believes that Kuiper et al. and Griesen et al. are properly combined a prime facie case of obviousness still fails because not all the the claimed elements are taught. This response has been thoroughly reviewed but not found persuasive because it is not obvious to try when there is a reasonable expectation of success because the ordinary artisan would be motivated to use fluorescent-labeled probes to eliminate the use of radioactivity, as fluorescence in non-radioactive. The ordinary artisan would have had a reasonable expectation of success that the use of fluorescent-labeled probes to detect pathogens could be used in the method of Greisen et al. because Kuiper et al. teach the use of fluorescent-labeled probes hybridizing to a sample for the detection of pathogens. The ordinary artisan would have had a reasonable expectation of success that the use of co hybridizing probes in a single step could be used in the method of Greisen et al. because Greisen et al. teaches the use of panel of probes that would enable the use of a single CSF sample to obtain multiple probe hybridization results and form a more rapid and sensitive means of detecting bacteria in clinical samples.

The response asserts on page 11 that Kuiper and Griesen et al. fail to teach all the claimed elements. The response states that the examiner is mixing methods and that southern blot hybridization is not reflected in the applicants claimed embodiment. It is noted that claims recite

a method of hybridization of target and reference DNA on a plurality of arrayed elements which does not limit the method to a specific type of hybridization. The claims merely require hybridization on a solid support with arrayed elements and in the instant case Greisen teaches a hybridization on a solid support with arrayed elements by southern plot.

The response further states that the examiner admits that Greisen et al. does not teach co-hybridization target and reference DNA in a single step and asserts that the examiner points to nothing in Kuiper that teaches co-hybridizing a target and reference DNA in a single step. This response has been reviewed but not found persuasive as the claims do not require co-hybridization in a single step, the claims merely require hybridization of target DNA and reference DNA to a plurality of arrayed elements.

The response asserts that neither Greisen or Kuiper et al. teach calculating the ratio of target and reference DNA labels that identify bacterial species. This response has been thoroughly reviewed but not found persuasive. The claims are broadly drawn to providing amplified genomic sequences, labeled target DNA with a fluorescent dye, labeled reference DNA with a fluorescent dye, and calculating the ratio of target fluorescent signal and reference fluorescent signal. Kuipers et al. teaches multiplexing of hybridization by fluorescently labeled cDNA and detecting the signals by confocal laser scanning (calculating the ratio of hybridization signal) and furthermore Kuipers et al. teaches differentially labeling two difference cDNA strains (see column 2, 1st paragraph, page 512). Kuiper further teaches differentially fluorescent-labeled wild type and mutant cDNA to allow for multiplexing. As stated in the rejection of record, Kuiper et al. does not teach the use of at least four strains of reference bacterial species, however Kuiper et al. in view of Greisen et al. does teach modifying the method of using differentially

labeled cDNA probes on a microarray as taught by Kuiper to include 12 different probes of seven reference bacterial species, as taught by Greisen to test for at least seven bacterial species causing meningitis. Therefore, Kuiper et al. and Greisen et al. teach the claimed invention

The response asserts on page 12, that the examiner does not teach any expectation of success. The response asserts that the cited reference do not explicitly predict the success for the claimed embodiment and they do not provide any reasonable expectation of success. The response states that none of the references demonstrate the identification of bacterial species using a simple hybridization ratio. This response has been thoroughly reviewed but not found persuasive. It is noted that, the state of the art for hybridization assays on an array was well established at the tine the invention was made as both Kuiper and Greisen teach hybridization assays on arrays. As stated above, Kuiper et al. teaches calculating the ratio of two differentially fluorescent labeled wild type and mutant cDNA to allow for multiplexing. Therefore, Kuiper et al. in view of Greisen et al. does teach modifying the method of using differentially labeled cDNA probes on a microarray as taught by Kuiper to include 12 different probes of seven reference bacterial species, as taught by Greisen to test for at least seven bacterial species causing meningitis. Therefore, Kuiper et al. and Greisen et al. teach the claimed invention.

The response asserts unexpected results, however, applicant does not provide any evidence of unexpected results. As stated in MPEP 2144, showing of unexpected results must be based on evidence, not argument or speculation. This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.

Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:
(1) prior to a final rejection,
(2) before appeal in an application not having a final rejection, or
(3) after final rejection and submitted
(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or
(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or
(iii) under 37 CFR 1.129(a).

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

11. Claims 6 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuiper et al. (Current Opinion in Biotechnology, 1999, 10:511-516) and Greisen et al. (J.Clin. Microbial. 1994, vol. 32, pp 335-351) as applied to claims 1-5, 7-13, and 15 above, and further in view of Arfin et al.. (J. Biol. Chem. 2000, vol. 275, pp. 29672-29684). This rejection was previously presented in section 7 of the previous office action mailed 07/01/2005 and is reiterated below.

The method of Kuiper et al. and Greisen et al. is set forth in section 6 above. Kuiper et al. and Greisen et al. do no teach statistical analysis in calculating the target signal to reference signal hybridization ratio at each array element.

Arfin et al. teach replication and appropriate statistical analysis is required for determining the accuracy of DNA microarray measurements. Arfin et al. teach that thousands of measurements are obtained from a single experiment using DNA microarrays experiments and in order to interrupt data from experiments it is necessary to employ statistical methods capable of

distinguishing chance occurrences from biologically meaningful data (see page 29676, 1st column, last paragraph). Arfin et al. teach using a t test to evaluate the difference between the means of two groups employing the variance within groups as an error term. Arfin et al. teach using the t test to determine statistical differences among different filters hybridized with the same RNA of the same genotype as well as differences among different RNA preparations of the same genotype hybridized to the same filters (see page 29674, 2nd column, 3rd paragraph).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Kuiper et al. and Greisen et al. of identifying bacteria using a microarray to include statistical analysis of the data as taught by Arfin et al. The ordinary artisan would have been motivated to improve the method of Kuiper et al. and Greisen et al. to include statistical analysis of the data obtained by the microarray analysis because Arfin et al. teach replication and appropriate statistical analysis is required for determining the accuracy of DNA microarray measurements. Furthermore Arfin et al. teach that thousands of measurements are obtained from a single experiment using DNA microarrays experiments and in order to interrupt data from experiments it is necessary to employ statistical methods capable of distinguishing chance occurrences from biologically meaningful data, therefore, the ordinary artisan would have had a reasonable expectation of success of using statistical data analysis in the method of Kuiper et al. and Greisen et.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Response to Arguments

12. The response states on page 12-13 of the response mailed 03/28/2007 that because the arguments and amendment place claims 1 and 9 in condition for allowance applicants submit that claims 6 and 14 are also not in condition for allowance. This response has been thoroughly reviewed but not found persuasive. Neither the amendment to the claims nor the arguments presented put the claims in condition for allowance.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Sarae Bausch
Examiner
Art Unit 1634

JEANINE A. GOLDBERG
PRIMARY EXAMINER
6/11/07